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 NEWS 15 AUG 09 INSPEC enhanced with 1898-1968 archive  
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 NEWS 17 AUG 30 CA(SM)/CAplus(SM) Austrian patent law changes  
 NEWS 18 SEP 11 CA/CAplus enhanced with more pre-1907 records

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 MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),  
 AND CURRENT DISCOVER FILE IS DATED 26 JUNE 2006.

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 MOST RECENT UPDATE WEEK: 200636 <200636/EW>  
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 (last updated April 10, 2006) <<<

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=> s CPT-11 or CPT11 or CPT () 11

2966 CPT  
 90 CPTS  
 3003 CPT  
 (CPT OR CPTS)  
 834457 11  
 473 CPT-11  
 (CPT(W)11)  
 22 CPT11  
 2966 CPT  
 90 CPTS  
 3003 CPT

(CPT OR CPTS)  
834457 11  
473 CPT (W) 11  
L1 486 CPT-11 OR CPT11 OR CPT (W) 11

=> s pretarget?  
L2 641 PRETARGET?

=> s 11 and 12  
L3 17 L1 AND L2

=> s 13 not py>1998  
791952 PY>1998  
L4 1 L3 NOT PY>1998

=> d ibib 1

L4 ANSWER 1 OF 1 PCTFULL COPYRIGHT 2006 Univentio on STN  
ACCESSION NUMBER: 1997041898 PCTFULL ED 20020514  
TITLE (ENGLISH): TARGETED COMBINATION IMMUNOTHERAPY OF CANCER  
TITLE (FRENCH): IMMUNOTHERAPIE-CIBLE ASSOCIEE CONTRE LE CANCER  
INVENTOR(S): GRIFFITHS, Gary, L.;  
HANSEN, Hans, J.  
PATENT ASSIGNEE(S): IMMUNOMEDICS, INC.;  
GRIFFITHS, Gary, L.;  
HANSEN, Hans, J.  
LANGUAGE OF PUBL.: English  
DOCUMENT TYPE: Patent  
PATENT INFORMATION:

NUMBER	KIND	DATE
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WO 9741898	A1	19971113

DESIGNATED STATES

W:

AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE  
ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS  
LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG  
SI SK TJ TM TR TT UA UG US UZ VN YU GH KE LS MW SD SZ  
UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR  
GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML  
MR NE SN TD TG

APPLICATION INFO.: WO 1997-US7395 A 19970502  
PRIORITY INFO.: US 1996-60/017,011 19960503

=> d kwic

L4 ANSWER 1 OF 1 PCTFULL COPYRIGHT 2006 Univentio on STN

DETD . . . converted to the active metabolite which kills the tumor. Examples of such enzyme-prodrug binding partners are I antibody-carboxypeptidase G2 and topoisomerase-inhibiting prodrug CPT-11; beta-lactamase and cephalosporin-doxorubicin; alkaline phosphatase and etoposide phosphate; carboxypeptidase G2 and glutamic acid derivative of benzoic acid mustard; and beta-glucuronidase and the glucuronide. . .

5,525,338, herein incorporated in its entirety by reference, discloses the use of secondary targeted antibodies within pretargeting protocols. In this embodiment, the use of biotin-avidin recognition is supplemented by antibody(3) recognition of the same or a different epitope on the. . .

```
=> s antibody (2W) enzyme
      77341 ANTIBODY
      76760 ANTIBODIES
      91010 ANTIBODY
          (ANTIBODY OR ANTIBODIES)
      108842 ENZYME
      91174 ENZYMES
      128660 ENZYME
          (ENZYME OR ENZYMES)
L5      6489 ANTIBODY (2W) ENZYME
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=> d his
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(FILE 'HOME' ENTERED AT 08:50:00 ON 14 SEP 2006)
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FILE 'PCTFULL' ENTERED AT 08:50:13 ON 14 SEP 2006
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L1      486 S CPT-11 OR CPT11 OR CPT () 11
L2      641 S PRETARGET?
L3      17 S L1 AND L2
L4      1 S L3 NOT PY>1998
L5      6489 S ANTIBODY (2W) ENZYME
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```
=> s 15 and 11
L6      31 L5 AND L1
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=> s 16 not py>1998
      791952 PY>1998
L7      0 L6 NOT PY>1998
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=> d kwic 16
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L6      ANSWER 1 OF 31      PCTFULL      COPYRIGHT 2006 Univentio on STN
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DETD . . . (TELCYTATM);
acetogenins (especially bullatacin and bullatacinone); delta
tetrahydrocannabinol (dronabinol, MARINOLO);
beta-lapachone; lapachol; colchicines; betulinic acid; a camptothecin
(including the synthetic analogue
topotecan (HYCANTINID), CPT-11 (irinotecan,
CAMPTOSAR), acetylcamptothecin, scoplectin, and 9-
aminocamptothecin); bryostatin; callystatin; CC-1065 (including its
adozelesin, carzelesin and bizelesin
synthetic analogues); podophyllotoxin; podophyllinic acid; teniposide;.
```

```
. . .
to a cytotoxic polypeptide. Other insertional variants of the antibody
molecule include the fusion to the N- or C-terminus of the
antibody to an enzyme (e.g. for ADEPT) or a
polypeptide which increases the serum half-life of the antibody.
```

```
=> s antibody (3W) enzyme
      77341 ANTIBODY
      76760 ANTIBODIES
      91010 ANTIBODY
          (ANTIBODY OR ANTIBODIES)
      108842 ENZYME
      91174 ENZYMES
      128660 ENZYME
          (ENZYME OR ENZYMES)
L8      8842 ANTIBODY (3W) ENZYME
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=> s 18 and 11
L9      42 L8 AND L1
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=> s 19 not py>1998  
791952 PY>1998  
L10 0 L9 NOT PY>1998

=> s enzyme (3W) antibod?  
108842 ENZYME  
91174 ENZYMES  
128660 ENZYME  
(ENZYME OR ENZYMES)  
91058 ANTIBOD?  
L11 7359 ENZYME (3W) ANTIBOD?

=> s 111 and 11  
L12 31 L11 AND L1

=> s 112 not py>1999  
724392 PY>1999  
L13 1 L12 NOT PY>1999

=> d kwic

L13 ANSWER 1 OF 1 PCTFULL COPYRIGHT 2006 Univentio on STN

DETD Structure-Based Classes  
1. Fluoropyrimidines  
2. Pyrimidine Nucleosides  
3. Purines  
4. Platinum Analogues  
5. Anthracyclines/Anthracenediones  
6. Podophyllotoxins  
7. Camptothecins  
B. Hormones and Hormonal Analogues  
9. Enzymes, Proteins and Antibodies  
10. Vinca Alkaloids  
11. Taxanes  
Mechanism-Based Classes  
1. Antihormonals  
2. Antifolates  
4  
. Antimicrotubule Agents  
4. Alkylating Agents (Classical and Non-Classical)  
5. Antimetabolites  
6. Antibiotics  
7. Topoisomerase Inhibitors  
8. Antivirals  
9. Miscellaneous Cytotoxic. . .  
. . .  
103;  
8. Hormones and Hormonal Analogues- Diethylstilbestrol,  
Tamoxifen, Toremefine, Tolmudex, Thymitaq, Flutamide,  
Bicalutamide, Finasteride, Estradiol, Trioxifene,  
Droloxifene, Medroxyprogesterone Acetate, Megesterol Acetate,  
Aminoglutethimide, Testolactone and others;  
9. Enzymes, Proteins and Antibodies- Asparaginase,  
Interleukins, Interferons, Leuprolide, Pegaspargase, and  
others;  
10. Vinca Alkaloids- Vincristine, Vinblastine,  
Vinorelbine, Vindesine;  
11. Taxanes- Paclitaxel, Docetaxel, and others.  
. . .  
since this discovery to  
developing water soluble camptothecin derivatives which  
remained in their active lactone form. Along these lines, the  
25  
recently approved Irinotecan (CPT-11) and Topotecan

were  
developed. Irinotecan is a water soluble prodrug of the  
highly active, highly lipophilic derivative of CPT known as  
SN38 (10-hydroxy. . .

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FILE 'PCTFULL' ENTERED AT 08:50:13 ON 14 SEP 2006

L1 486 S CPT-11 OR CPT11 OR CPT () 11  
L2 641 S PRETARGET?  
L3 17 S L1 AND L2  
L4 1 S L3 NOT PY>1998  
L5 6489 S ANTIBODY (2W) ENZYME  
L6 31 S L5 AND L1  
L7 0 S L6 NOT PY>1998  
L8 8842 S ANTIBODY (3W) ENZYME  
L9 42 S L8 AND L1  
L10 0 S L9 NOT PY>1998  
L11 7359 S ENZYME (3W) ANTIBOD?  
L12 31 S L11 AND L1  
L13 1 S L12 NOT PY>1999

=> s antibod? (3W) enzyme

91058 ANTIBOD?  
108842 ENZYME  
91174 ENZYMES  
128660 ENZYME  
(ENZYME OR ENZYMES)

L14 8855 ANTIBOD? (3W) ENZYME

=> s l14 and l1

L15 42 L14 AND L1

=> s l15 not py>1999

724392 PY>1999

L16 1 L15 NOT PY>1999

=> d ibib kwic

L16 ANSWER 1 OF 1 PCTFULL COPYRIGHT 2006 Univentio on STN  
ACCESSION NUMBER: 1999042593 PCTFULL ED 20020515  
TITLE (ENGLISH): COMPOSITIONS AND METHODS FOR SENSITIZING AND INHIBITING  
GROWTH OF HUMAN TUMOR CELLS  
TITLE (FRENCH): COMPOSITIONS ET PROCEDES SERVANT A SENSIBILISER ET A  
INHIBER LA CROISSANCE DE CELLULES CANCEREUSES HUMAINES  
INVENTOR(S): DANKS, Mary, K.;  
POTTER, Philip, M.;  
HOUGHTON, Peter, J.  
PATENT ASSIGNEE(S): ST. JUDE CHILDREN'S RESEARCH HOSPITAL;  
DANKS, Mary, K.;  
POTTER, Philip, M.;  
HOUGHTON, Peter, J.  
LANGUAGE OF PUBL.: English  
DOCUMENT TYPE: Patent  
PATENT INFORMATION:

NUMBER	KIND	DATE
-----		
WO 9942593	A1	19990826

DESIGNATED STATES

W:

AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE  
ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR  
KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT

RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU  
 ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ  
 TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT  
 SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 1999-US3171 A 19990212  
 PRIORITY INFO.: US 1998-60/075,258 19980219

DETD CPT-11 (irinotecan, 7-ethyl [4-(1-piperidino) piperidinolcarbonyloxycamptothecin) is a prodrug currently under investigation for the treatment of cancer that is converted to the active drug. . .

5 49:5077-5082). The specific enzyme responsible for activation in vivo of CPT-11 has not been identified, although serum or

liver homogenates from several mammalian species have been shown to contain activities that convert CPT-11 to SN-38

(Tsuji, T. et al. 1991. J. Pharmacobiol. Dynamics 14:341-349; Senter, P.D. et al. 1996. Cancer Res. 56:1471-1474; Satoh, T.

In fact, SN-38 can be detected in the plasma of animals and humans minutes after the administration of CPT-11

(Stewart, C.F. et al. 1997. Cancer Chemother. Pharmacol. 40:259-265; Kaneda, N. et al. 1990. Cancer Res. 50:1715-1720; Rowinsky, E.K. et al. 1994. Cancer. . .

of this class of enzymes has yet to be identified. A recent biochemical analysis of 13 CEs compared their ability to metabolize CPT-11 to SN

While the efficiency of conversion varied between enzymes, those isolated from rodents were the most efficient (Satoh, T. et al. 1994.. . .

EMBL databases, including a rat serum and rat liver microsomal CE. Interestingly, CEs purified from human tissues demonstrated the least efficient conversion of CPT-11 to SN-38, with less than 5% of the prodrug being

5 converted to active drug (Leinweber, F.J. 1987. Drug Metab.

In addition to metabolism to SN-38, in humans CPT-11 is also metabolized to a compound known as APC (Haaz, M.C. et al.

In preclinical studies, CPT-11 administered to immune-deprived mice bearing human tumor xenografts produces complete regression of glioblastomas, rhabdomyosarcomas (RMS), neuroblastomas, and colon adenocarcinomas (Houghton, P.J. et al. 1995. Cancer Chemother. Pharmacol. 36:393-403; Houghton, P.J. et al. 1993. Cancer Res. 53:2823-2829). However, maintenance of tumor regression in studies with CPT-11 appears

to be dependent upon drug scheduling, suggesting that viable tumor cells survive therapy (i.e., minimal residual disease (MRD)). These studies also showed a steep dose-response relationship between dose of drug administered and induction of tumor regression. For example, 20 mg of CPT-11 /kg/day

given daily for 5 days for two weeks produced complete regressions of Rh18 RMS xenografts, while 10 mg/kg/day given on the same schedule. . .

Similar effects were seen when mice bearing SJGC3A colon adenocarcinoma xenografts were treated with 40 mg CPT-11/kg compared to a 20 mg/kg dose.

Early clinical trials with CPT-11 indicate that the prodrug also has anti-tumor activity in vivo against many different types of solid tumors in humans. However, myelosuppression and secretory. . .

present invention, polynucleotides encoding a carboxylesterase enzyme or active fragments thereof and polypeptides encoded thereby which are capable of metabolizing the chemotherapeutic prodrug CPT-11 and its inactive metabolite APC to active drug SN-38 are disclosed. Use of this enzyme in combination with APC renders this inactive metabolite. . . invention and a disease-specific responsive promoter can be delivered to selected tumor cells to sensitize the tumor cells to the chemotherapeutic prodrug CPT-11

30 thereby inhibiting tumor cell growth.

Figure 5 is a linegraph comparing % cell survival, depicted on the Y-axis, at various concentrations of CPT-11, depicted on the X-axis. Control Cos7 cells (filled squares) are approximately 350-fold more sensitive to CPT-11 than Cos7 cell transfected with CE (filled triangles).

Figure 8 provides the chemical structures of CPT-11, APC and SN

Figure 9A, 9B, and 9C are linegraphs showing the responses of mice bearing Rh30 and RhHpIRESI.bbit rhabdosarcoma xenografts to CPT-11 treatment. Each line on each graph shows the growth of an individual tumor. The tumor growth rate is depicted on the Y-axis. . .

depicts cells expressing rabbit CE (RhHpIRESabbit) not treated with CPT Figure 9B depicts cells expressing rabbit CE (RhHpIRES,abbit) and then treated with CPT-11 and shows complete tumor regression, even out to 12 weeks. Figure 9C depicts control cells (Rh30) exposed to CPT-11 and shows initial regression but regrowth.

Figure 10 is a linegraph showing the effects of CPT-11 treatment on U373 glioblastoma xenografts expressing rabbit CE. Mice bearing xenografts were treated with CPT-11 (7.5 mg/kg for 5 days) for three treatment cycles. The tumor growth rate is depicted on the Y-axis in terms of tumor. . .

#### Detailed Description of the Invention

CPT-11 is a promising anti-cancer prodrug, that when given to patients, is converted to its active metabolite SN-38 by a human carboxylesterase. However,. . .

to compositions comprising a polynucleotide of the present invention which

have been found to be useful in sensitizing tumor cells to CPT-11 cytotoxicity by combination therapy of the prodrug and a CE enzyme. The present invention thus provides methods for sensitizing tumor cells to. . .

In addition, the rabbit CE demonstrated greater than 85% homology with human alveolar macrophage CE yet the latter enzyme failed to convert CPT-11 to SN-38 in mammalian cells. This indicates that while CEs may have a broad range of substrate specificities, the efficiency with which similar. . .

the SV40 origin of replication allowing plasmid amplification in cells expressing the large T antigen, such as Cos7. The IC<sub>50</sub> value for CPT-11 for cells expressing the CE was approximately B-80 fold, and most typically about 56 fold, less than that of the parent cell line thus indicating 35 that the enzyme has sensitized mammalian cells to CPT-11 (see Figure 5).

to sensitize the tumor cells to a chemotherapeutic prodrug. The ability of the combination of a rabbit CE of the present invention and CPT-11 to sensitize human tumor cells to CPT-11 was examined. Experiments were first performed to confirm that the metabolite produced by the activity of a CE of the present invention is. . .

to 5 units of CE that had been inactivated by heating produced no inhibition of cell growth. In contrast, reaction products of CPT-11 incubated with 1 to 5 units of active CE produced a 30-60% inhibition of cell growth. These data are consistent with the conversion of CPT-11 to SN-38 by CE in these cells.

The CE activity of extracts of the transfected cells was then determined. The IC<sub>50</sub> values for CPT-11 in Rh30 rhabdomyosarcoma cells that had been stably transfected with a rabbit liver CE cDNA of the present invention or the pIRES vector. . . alone were also determined. Cells transfected with the CE cDNA contained approximately 60-fold more CE activity than control cells. The IC<sub>50</sub> Of CPT-11 for Rh30pIRES cells (no CE cDNA) was  $4.33 \times 10^{-6}$  M while the IC<sub>50</sub> for the Rh30pIRES.,bbit cells was  $5.76 \times 10^{-7}$ . . . M. Therefore, the transfected cells were more than 8-fold more sensitive to CPT These data are consistent with an increased conversion of CPT-11 to SN-38 in 35 the cells transfected with a CE of the present invention.

CE of the present invention. These data confirm the unique ability of a CE of the present invention to activate the prodrug CPT-11, as well as to activate one of its metabolites. Further, experiments in U-373 cells that express a CE of the present invention showed. . .

In vivo efficacy of the CE of the present invention to



sensitize tumor cells to CPT-11 has also been demonstrated in two different types of tumor cells. Experiments conducted in a mouse model demonstrate that a CE of. . . for rabbit CE was maintained for at least 12 weeks. Importantly, tumors were advanced (greater than 1 CM<sup>3</sup> in volume) before treatment with CPT-11 began. As depicted in Figure 9B, tumors in mice expressing CE and treated with 2.5 mg CPT-11 /kg/day 25 for five days each week for two weeks (one cycle of therapy), repeated every 21 days for a total of three. . . not regrow during the 12 weeks of the study. In contrast, tumors that did not express the CE regressed only transiently with CPT-11 treatment, with 30 regrowth occurring within one week after CPT-11 treatment stopped (see Figure 9C).

In a second set of experiments, human U373 glioblastoma xenografts that express rabbit liver CE were shown to be more sensitive to CPT-11 than xenografts transfected with a control 35 plasmid (no rabbit CE). Xenografts established from cells - 22 transfected with the plasmid encoding rabbit. . .

Thus, these data support the use of the combination of polynucleotide encoding a CE of the present invention and CPT-11 to reduce the amount of CPT-11 needed to produce inhibition of tumor cell growth, or to sensitize the tumor cells to CPT-11. These data also support the use of the present invention 10 to allow for decreased dosage with CPT-11 in cancer patients, thus reducing the likelihood of dose-limiting toxicity.

promoter. The vectors can then be injected into the site of tumor removal along with systemic administration of a prodrug such as CPT-11 to inhibit the recurrence of tumors due to residual tumor cells present after surgical resection of a tumor.

Another method for delivering CEs to selected tumor cells involves antibody direct enzyme prodrug therapy (ADEPT).

a molecule such as rabbit liver CE. Cellular internalization of the complex and release of active CE would be achieved, leading to CPT-11 activation that is specific for cells expressing the marker antigen.

25 Both the secreted and the endoplasmic reticulum-localized protein can convert CPT-11 to SN-38; therefore, the potential exists for a bystander effect from cells expressing the secreted enzyme. A similar bystander effect has been demonstrated. . .

Extracellular activation of CPT-11 may result in more efficient eradication of MRD in that uninfected neighboring

tumor cells would be killed by exogenously produced SN  
35 Gene therapy protocols with a secreted CE in combination with  
CPT-11 may therefore be more appropriate for the  
elimination

of residual tumor tissue. Accordingly, in this embodiment,

- 24 -

it may be preferred.

the plasma. Attachment of a CE of the present  
invention to the cell surface should result in local  
15 extracellular activation of CPT-11 to SN-38 and  
enhance local  
cell kill. Purging bone marrow of contaminating tumor cells  
will be accomplished by an intracellular enzyme, whereas  
eradication of MRD is better achieved by an enzyme that  
activates CPT-11 at an extracellular location.

CEs of the present invention cleave the COOC bond  
present as an ester linkage in CPT-11 to generate  
SN-38 (see  
Figure 8). Since this enzyme may also catalyze the activation  
of other compounds that contain such a linkage,

#### EXAMPLES

##### Example 1: Identification of CEs

A CE enzyme suitable for converting CPT-11 to the  
active  
form, SN-38 was identified by testing a variety of samples.

CEs were commercially  
available, several of these were also tested for their ability  
to metabolize CPT Both rabbit and pig liver CEs  
metabolized CPT-11 efficiently. The commercially  
available  
pig CE contained several proteins. However, the major bands  
were very similar in molecular weight and did not.

activity of rabbit CE

The in vitro activity of rabbit liver CE was examined  
in tumor cell lines. The growth inhibition of CPT-11  
was

compared in cells with and without active rabbit CE. The  
cells used were Rh30 cells (lo') that had been electroporated  
with 20.

In the first assay, CPT-11 was pre-incubated with  
rabbit  
liver CE to produce SN-38 prior to exposure of the cells to  
drug. specifically, 0.5 to 5 units of CE were incubated with  
1  $\mu$ M CPT-11 at 37°C in DMEM medium for 2 hours. Each  
reaction  
mixture was then filter-sterilized and Rh30 cells were exposed  
to drug for. . . was replaced  
with drug-free medium containing serum. Enzyme that had been  
inactivated by boiling for five minutes prior to incubation  
with drug or CPT-11 to which no enzyme had been  
added were  
used as negative controls. Cells were allowed to grow for 3  
cell doubling times.

the conversion of o-nitrophenyl acetate to  
o-nitrophenol. Further, the Rh30pIRES cells transfected with  
rabbit CE were greater than 8-fold more sensitive to CPT-  
11  
than controls, as shown by a decrease in the IC<sub>50</sub> values.

Therefore, Rh30 cells stably transfected with rabbit CE were more sensitive to growth inhibition by CPT-11 than cells that did not contain the cDNA for rabbit CE.

- 30 -

Example 5: Rabbit CE activates APC, a novel prodrug  
In addition to efficiently converting CPT-11 to the active compound SN-38, experiments were also performed demonstrating the ability of rabbit liver CE to convert the inactive metabolic end product. . .

in the prevention of MRD. In this model, treatment of immune-deprived mice, i.e., SCID mice, bearing human NB-1691 xenografts with 10 mg/kg CPT-11 daily for 5 days on two consecutive weeks results in complete regression of the tumor. However, within 4-6 weeks, tumors are palpable. . .

identical fashion with Rh30 cells not transfected with the plasmid. When the tumors reached a size of approximately 1 cm<sup>3</sup>, 2.5 mg CPT-11/kg/day was administered five days each week for two weeks (one cycle of therapy), repeated every 21 days for a total of three. . .

In contrast, tumors not expressing the CE regressed only transiently,, regrowing within one week after CPT-11 treatment had stopped (Figure 9C).

Cells were injected subcutaneously into the flanks of the SCID mice. When tumors reached approximately 1 CM<sup>3</sup> in size, CPT-11 was administered daily for five days each week as described above, for three cycles, at a dose of 7.5 mg/kg/day.

implantation in this model during the 4 to week period when tumors are not present, followed by treatment with low doses of CPT-11, also demonstrates the effectiveness of the virus at preventing MRD. Typically, 5 since tumor regression is complete 3 weeks after commencing treatment with CPT-11, adenovirus/drug administration begins at week 4. In initial experiments, adenovirus is administered on Monday, Wednesday, Friday and CPT-11 is given daily on Tuesday through Saturday for two cycles. This permits determination of the most tolerated, effective schedule and dosage of adenovirus and CPT-11 administration to produce the longest delay of recurrent disease. These results are used to determine correct dosage for treatment of human MRD.. . .

bone marrow of these same animals contains neuroblastoma cells. The success of ex vivo purging of bone marrow with the rabbit liver CE/CPT-11 combination is demonstrated by transplanting purged bone marrow into lethally irradiated mice. If mice remain disease free for extended periods of time, this. . .

- 33 -

Example 8: Treatment of Minimal Residual Disease (MRD) in humans

The rabbit CE in combination with CPT-11 or other prodrugs activated by 'this enzyme is used to purge bone marrow of residual tumor cells prior to autologous bone marrow transplants. . .

Nature Med. 3:639-645). CPT-11 is administered over the next one to six weeks to elicit tumor selective cell kill. Doses 20 and schedules of CPT-11 are determined in clinical trials of CPT-11 by itself and in human xenograft model systems to produce maximal tumor effect.

majority of hematopoietic progenitor cells. Two days

- 34 -

following adenoviral transduction, cells are exposed for two hours to a range of CPT-11 concentrations, usually varying from 50 nM to 100 pM. Two days after exposure to drug, the marrow sample is harvested and stored. . .

CLMEN 13 The method of claim 12 wherein the chemotherapeutic prodrug is selected from a group consisting of CPT-11 and APC.

15 The method of claim 14 wherein the chemotherapeutic prodrug is selected from a group consisting of CPT-11 and APC.

=> file caplus  
COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
15.57	15.78

FULL ESTIMATED COST

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=> s antibod? (3W) enzyme  
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783759 ENZYME

```
=> s CPT-11/cn
    REGISTRY INITIATED
Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.
```

```
=> s CPT11/cn
    REGISTRY INITIATED
Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.
```

```
=> s cpt 11/cn\  
'CN\' IS NOT A VALID FIELD CODE  
L22          0 CPT 11/CN\  
          0
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```
=> s cpt 11/cn
    REGISTRY INITIATED
Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.
```

=> d his

(FILE 'HOME' ENTERED AT 08:50:00 ON 14 SEP 2006)

FILE 'PCTFULL' ENTERED AT 08:50:13 ON 14 SEP 2006

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L1          486 S CPT-11 OR CPT11 OR CPT () 11
L2          641 S PRETARGET?
L3          17 S L1 AND L2
L4           1 S L3 NOT PY>1998
L5         6489 S ANTIBODY (2W) ENZYME
L6          31 S L5 AND L1
L7           0 S L6 NOT PY>1998
L8        8842 S ANTIBODY (3W) ENZYME
L9          42 S L8 AND L1
L10          0 S L9 NOT PY>1998
L11       7359 S ENZYME (3W) ANTIBOD?
L12         31 S L11 AND L1

```

L13 1 S L12 NOT PY>1999  
L14 8855 S ANTIBOD? (3W) ENZYME  
L15 42 S L14 AND L1  
L16 1 S L15 NOT PY>1999

FILE 'CAPLUS' ENTERED AT 08:55:25 ON 14 SEP 2006  
L17 6081 S ANTIBOD? (3W) ENZYME  
S CPT-11/CN

FILE 'REGISTRY' ENTERED AT 08:55:50 ON 14 SEP 2006  
L18 0 S CPT-11/CN

FILE 'CAPLUS' ENTERED AT 08:55:51 ON 14 SEP 2006  
L19 0 S L18  
S CPT11/CN

FILE 'REGISTRY' ENTERED AT 08:55:58 ON 14 SEP 2006  
L20 0 S CPT11/CN

FILE 'CAPLUS' ENTERED AT 08:55:59 ON 14 SEP 2006  
L21 0 S L20  
L22 0 S CPT 11/CN\  
S CPT 11/CN

FILE 'REGISTRY' ENTERED AT 08:56:12 ON 14 SEP 2006  
L23 1 S CPT 11/CN

FILE 'CAPLUS' ENTERED AT 08:56:12 ON 14 SEP 2006  
L24 888 S L23

=> s 124 and 117  
L25 7 L24 AND L17

=> s 117 (L) 124  
L26 1 L17 (L) L24

=> d ibib

L26 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 2002:236399 CAPLUS  
DOCUMENT NUMBER: 136:268117  
TITLE: Antibody-enzyme conjugates for increasing the  
target-specific toxicity of a chemotherapy drug  
INVENTOR(S): Griffiths, Gary L.; Hansen, Hans J.  
PATENT ASSIGNEE(S): Immunomedics, Inc., USA  
SOURCE: U.S., 8 pp.  
CODEN: USXXAM  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 2  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6361774	B1	20020326	US 1999-399221	19990917
US 2002114808	A1	20020822	US 2002-66782	20020206
PRIORITY APPLN. INFO.:			US 1998-101039P	P 19980918
			US 1999-399221	A3 19990917
REFERENCE COUNT:	32	THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT		

=> d 125 ibib 1-7

L25 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:546856 CAPLUS  
 DOCUMENT NUMBER: 143:73869  
 TITLE: Design and sequences of human butyrylcholinesterase variants that alter the activity of anticancer agents and the use in cancer treatment  
 INVENTOR(S): Watkins, Jeffry D.; Pancook, James D.  
 PATENT ASSIGNEE(S): USA  
 SOURCE: U.S. Pat. Appl. Publ., 60 pp.  
 CODEN: USXXCO  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005136044	A1	20050623	US 2003-728723	20031204
PRIORITY APPLN. INFO.:			US 2003-728723	20031204

L25 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:817401 CAPLUS  
 DOCUMENT NUMBER: 141:289026  
 TITLE: Rabbit liver carboxylesterase capable of activating chemotherapeutic prodrug and thereby sensitizing and inhibiting growth of human tumor cells  
 INVENTOR(S): Danks, Mary K.; Potter, Philip M.; Houghton, Peter J.  
 PATENT ASSIGNEE(S): St. Jude Children's Research Hospital, USA  
 SOURCE: U.S., 39 pp., Cont.-in-part of WO 99 42,593.  
 CODEN: USXXAM  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 2  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6800483	B1	20041005	US 2000-595682	20000616
WO 9942593	A1	19990826	WO 1999-US3171	19990212
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2004259829	A1	20041223	US 2004-858271	20040601
PRIORITY APPLN. INFO.:			US 1998-75258P	P 19980219
			WO 1999-US3171	A2 19990212
			US 2000-595682	A1 20000616
REFERENCE COUNT:	25	THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT		

L25 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:453053 CAPLUS  
 DOCUMENT NUMBER: 141:1228  
 TITLE: Use of multi-specific, non-covalent complexes for targeted delivery of therapeutics  
 INVENTOR(S): Griffiths, Gary L.; Govindan, Serengulam V.; Hansen, Hans J.  
 PATENT ASSIGNEE(S): Immunomedics, Inc., USA; McCall, John Douglas  
 SOURCE: PCT Int. Appl., 44 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004045642	A1	20040603	WO 2003-GB4994	20031117
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
CA 2505717	AA	20040603	CA 2003-2505717	20031117
AU 2003283599	A1	20040615	AU 2003-283599	20031117
US 2004166115	A1	20040826	US 2003-714391	20031117
EP 1560596	A1	20050810	EP 2003-775576	20031117
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK			
JP 2006514627	T2	20060511	JP 2004-552884	20031117
PRIORITY APPLN. INFO.:			US 2002-426379P	P 20021115
			WO 2003-GB4994	W 20031117

L25 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 2003:584407 CAPLUS  
DOCUMENT NUMBER: 139:358244  
TITLE: Carboxylesterase-mediated sensitization of human tumor cells to CPT-11 cannot override ABCG2-mediated drug resistance  
AUTHOR(S): Wierdl, Monika; Wall, Amelia; Morton, Christopher L.; Sampath, Janardhan; Danks, Mary K.; Schuetz, John D.; Potter, Philip M.  
CORPORATE SOURCE: Department of Molecular Pharmacology, St. Jude Children's Research Hospital, Memphis, TN, USA  
SOURCE: Molecular Pharmacology (2003), 64(2), 279-288  
CODEN: MOPMA3; ISSN: 0026-895X  
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 2002:236399 CAPLUS  
DOCUMENT NUMBER: 136:268117  
TITLE: Antibody-enzyme conjugates for increasing the target-specific toxicity of a chemotherapy drug  
INVENTOR(S): Griffiths, Gary L.; Hansen, Hans J.  
PATENT ASSIGNEE(S): Immunomedics, Inc., USA  
SOURCE: U.S., 8 pp.  
CODEN: USXXAM  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 2  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6361774	B1	20020326	US 1999-399221	19990917
US 2002114808	A1	20020822	US 2002-66782	20020206



PRIORITY APPLN. INFO.:

US 1998-101039P P 19980918  
US 1999-399221 A3 19990917

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:549389 CAPLUS

DOCUMENT NUMBER: 131:165300

TITLE: Rabbit liver carboxylesterase capable of activating  
chemotherapeutic prodrug and thereby sensitizing and  
inhibiting growth of human tumor cells

INVENTOR(S): Danks, Mary K.; Potter, Philip M.; Houghton, Peter J.

PATENT ASSIGNEE(S): St. Jude Children's Research Hospital, USA

SOURCE: PCT Int. Appl., 70 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9942593	A1	19990826	WO 1999-US3171	19990212
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2320808	AA	19990826	CA 1999-2320808	19990212
AU 9928679	A1	19990906	AU 1999-28679	19990212
AU 755251	B2	20021205		
EP 1054979	A1	20001129	EP 1999-909488	19990212
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002504340	T2	20020212	JP 2000-532533	19990212
US 6800483	B1	20041005	US 2000-595682	20000616
US 7018631	B1	20060328	US 2000-622568	20000831
US 2004259829	A1	20041223	US 2004-858271	20040601

PRIORITY APPLN. INFO.:

US 1998-75258P A2 19980219  
WO 1999-US3171 W 19990212  
US 2000-595682 A1 20000616

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:277438 CAPLUS

DOCUMENT NUMBER: 131:97098

TITLE: Comparison of activation of CPT-11 by rabbit and human  
carboxylesterases for use in enzyme/prodrug therapy

AUTHOR(S): Danks, Mary K.; Morton, Christopher L.; Krull, Erik J.; Cheshire, Pamela J.; Richmond, Lois B.; Naeve, Clayton W.; Pawlik, Cynthia A.; Houghton, Peter J.; Potter, Philip M.

CORPORATE SOURCE: Department of Molecular Pharmacology [M. K. D., C. L. M., E. J. K., P. J., St. Jude Children's Research Hospital, Memphis, TN, 38105, USA

SOURCE: Clinical Cancer Research (1999), 5(4), 917-924

CODEN: CCREF4; ISSN: 1078-0432

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=>

---Logging off of STN---

=>

Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

10.04

46.70

STN INTERNATIONAL LOGOFF AT 08:57:41 ON 14 SEP 2006